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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,766	12/03/2004	Ira H Pastan	015280-464200US	2791
20350 7590 01/17/2008 TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834				
			EXAMINER BLANCHARD, DAVID J	
			ART UNIT 1643	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/516,766	Applicant(s) PASTAN ET AL.	
	Examiner David J. Blanchard	Art Unit 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 October 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20, 27-45 and 52-82 is/are pending in the application.
- 4a) Of the above claim(s) 27-37, 52-65 and 76-80 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 66 is/are allowed.
- 6) ☒ Claim(s) 1-4, 7-9, 12-14, 18-20, 38, 40-45, 67 and 81-82 is/are rejected.
- 7) ☒ Claim(s) 5, 6, 10, 11, 15-17 and 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant is advised that claims 68-75 have been omitted from the claims filed 12 October 2007. Applicant is reminded that each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. See 37 CFR 1.121(c). For the purposes of this Office Action claims 68-75 are interpreted as cancelled. A canceled claim can be reinstated only by a subsequent amendment presenting the claim as a new claim with a new claim number. See MPEP 714(II)(C)(D) "Claim Numbering".
2. Claims 21-26, 46-51 and 68-75 have been cancelled.

Election/Restrictions

3. Applicant's election with traverse of the invention of Group I, claims 1-20, 38-45, 66-67, 81 and 82 in the reply filed on 12 October 2007 is acknowledged. The traversal is on the grounds that cleavage of CD30 leaves a stalk proximal to the cell surface and since the existence of a stalk was not known, it could not be known that antibodies that bind to the stalk are advantageous compared to antibodies that bind to other portions of the antigen. Applicant points to Figure 1 of the instant application which shows that antibody HeFi-1 does not map to the stalk region. Applicants' arguments have been fully considered but are not found persuasive. The examiner maintains that Lemke et al still teaches an antibody that binds to the stalk of CD30, or to an epitope destroyed upon cleavage of soluble CD30 from intact CD30 (see art rejection below). Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features, meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. Hence, in view of Lemke et al, the special technical feature of claim 1 is not special and the groups are not so linked as to form a general concept under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

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4. Claims 27-37, 52-65 and 76-80 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 12 October 2007.

5. Claims 1-20, 38-45, 66-67, 81 and 82 are under consideration.

Specification

6. The disclosure is objected to because of the following informalities:

a. Applicants' domestic priority benefit claim on the ADS filed 12/3/2004 is acknowledged, however, it is suggested that applicant amend the first line of the specification consistent with the ADS, i.e., the instant application is a 371 of PCT/US03/18373, filed 6/9/2003, and claims the benefit of U.S. Provisional Application No. 60/387,293, filed 6/7/2002 and U.S. Provisional Application No. 60/411,032, filed 9/16/2002. Applicant is reminded that the priority applications cannot be incorporated by reference after the original filing of the instant application.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

b. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 2-3, 8, 13 and 40-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 3, 8 and 13 are indefinite in the recitation "residues X to Y of CD30" in claim 3. The claims do not identify the sequence of CD30 and different CD30 molecules can have different sequences. Thus, the phrase "residues X to Y of CD30" is relative in nature and can have different meanings for different CD30 molecules. As written, one of skill in the art would not be reasonably apprised of the metes and bounds of the claims. Amending claim 3 to include the sequence identifier for CD30 (i.e., SEQ ID NO:1), thereby providing a point of reference that defines the claimed residues of CD30 would overcome this rejection.

b. Claims 2 and 40-41 are indefinite in the recitation "disulfide-stabilized recombinant variable region ("dsFv"). Those of skill in the art recognize that the Fv portion of an antibody comprises the heavy chain variable region and the light chain variable region (e.g., see Nagata et al (Clinical Cancer Research, 8(7):2345-2355, July 2002). Thus, one of skill in the art would not be reasonably apprised of the metes and bounds of a disulfide-stabilized recombinant variable region designated as "dsFv", since a dsFv comprises both the heavy and light chain variable regions of an antibody. Amending the claims to recite wherein the antibody is a disulfide-stabilized antibody ("dsFv") consistent with the knowledge of those skilled in the art would overcome the instant rejection.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 38, 40, 42-45, 67 and 81-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody comprising all 6 CDRs of antibody T6, T13, T25, T105, T201 or AC10, three from the heavy chain variable domain (VH) and three from the light chain variable domain (VL), wherein the antibody retains the CD30 specificity of the parental antibody, does not reasonably provide enablement for an antibody that does not contain a full set of 6 CDRs from the VH and the VL domains of antibody T6, T13, T25, T105, T201 or AC10 and do not bind CD30 as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to an antibody comprising at least one CDR selected from the VH or VL domain of antibody T6 (SEQ ID NO:2 or SEQ ID NO:15), T13 (SEQ ID NO:4 or SEQ ID NO:17), T25 (SEQ ID NO:7 or SEQ ID NO:22), T105 (SEQ ID NO:14 or SEQ ID NO:29), T201 (SEQ ID NO:38 or SEQ ID NO:39) or AC10 wherein the antibody is a disulfide-stabilized antibody ("dsFv") and compositions comprising the antibody is fused to a therapeutic moiety or a cytotoxin and kits comprising the antibody conjugated to a detectable label. Thus, the claim language encompasses antibodies which do not contain a full set of 6 CDRs, three from the VH domain and three from the VL domain from antibody T6, T13, T25, T105, T201 or AC10 and do not bind CD30.

The specification discloses only antibodies that specifically bind CD30 and comprise all 6 CDRs, three from the VH domain and three from the VL domain of antibody T6, T13, T25, T105, T201 or AC10 (see Examples). The specification does teach antibodies that do not contain all six CDRs, three from the VH domain and three from the VL domain of antibody T6, T13, T25, T105, T201 or AC10 that bind CD30. There are no working examples of antibodies comprising fewer than all six CDRs, three from the VH domain and three from the VL domain of antibody T6, T13, T25, T105, T201 or AC10 and bind CD30.

The state of the prior art is such that it is well established in the art that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope (Paul, *Fundamental Immunology*, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (*Proc. Natl. Acad. Sci. USA*, 79:1979-1983, March 1982). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman P. M. (*Research in Immunology*, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right

column). Additionally, Bendig (Methods: A Companion to Methods in Enzymology, 1995; 8:83-93) reviews that the general strategy for "humanizing" antibodies involves the substitution of all six CDRs from a rodent antibody that binds an antigen of interest, and that all six CDRs are involved in antigen binding (see entire document, but especially Figures 1-3). Similarly, the skilled artisan recognized a "chimeric" antibody to be an antibody in which both the heavy chain variable region (which comprises the three heavy chain CDRs) and the light chain variable region (which comprises the three light chain CDRs) of a rodent antibody are recombined with constant region sequences from a human antibody of a desired isotype (see entire document, but especially Figures 1-3). Thus, the state of the art recognized that it would be highly unpredictable that an antibody comprising less than all six CDRs of a parental antibody with a desired specificity would retain the antigen-binding function of the parental antibody. Thus, the minimal structure which the skilled artisan would consider predictive of the function of binding CD30/SEQ ID NO:1 includes six CDRs (three from the heavy chain variable region and three from the light chain variable region) from the same parental antibody in the context of framework sequences which maintain their correct spatial orientation have the requisite antigen-binding function. In addition, the skilled artisan recognized that single CDRs with the same amino acid sequence could be found in antibodies with diverse specificities. In particular, antibodies which have not yet undergone affinity maturation may still utilize germline heavy and light chain sequences. Between antibodies utilizing the same germline heavy or light chain gene the skilled artisan would expect to find that one or more of the heavy and/or light chain CDRs were the same as that of an antibody with a different specificity, particularly CDRs 1 and 2 which are germline encoded completely in the variable region. The same CDR may also occur in antibodies having somatic mutations that bind different antigens. Thus, it would be highly unpredictable that the instantly recited antibodies comprised of fewer than all six CDRs (three CDRs defined in the heavy chain variable region and three CDRs defined in the light chain variable region) of a particular reference antibody would have the same specificity as the reference antibody. Further, the antibody structure is not a random combination of heavy and light chain variable regions. The antibody paratope,

binds an epitope on an antigen. The paratope of the antibody is highly specific and provides for a specific three-dimensional structure in which the epitope of the antigen binds. The pocket is dependent on the specific primary structure of the complementary determining regions provided in a framework of other regions in a specific order. The specification does not describe nor enable the random combination of heavy and light chain variable regions or CDRs therefrom or CDR variants thereof to prepare an antibody having the requisite CD30 binding function. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

In view of the lack of the predictability of the art to which the invention pertains as evidenced by Paul W. E., Rudikoff et al, Colman P. M., and Bendig M. M., the lack of guidance and direction provided by applicant, and the absence of working examples, undue experimentation would be required to practice the claimed antibodies comprising fewer than all six CDRs from a reference antibody (i.e., antibody T6, T13, T25, T105, T201 or AC10) and which bind CD30 with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed antibodies and absent working examples providing evidence which is reasonably predictive that the claimed humanized 340 antibodies comprising fewer than all six CDRs from antibody T6, T13, T25, T105, T201 or AC10 bind CD30, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-4, 7-9, 12-14 and 18-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemke et al (WO 96/22384, 7/25/1996, cite) as evidenced by the specification and Nagata et al (Clinical Cancer Research, 8(7):2345-2355, July 2002).

Lemke et al teach anti-CD30 antibodies for the treatment of Hodgkin's disease, including HeFi-1 and M67, wherein the antibodies may be a scFv or dsFv and wherein the antibodies are conjugated or fused to a toxin, a chemotherapeutic or a radioisotope, wherein the toxin may be PE38 or PE40 (*Pseudomonas* exotoxin A), and Lemke et al teach pharmaceutical compositions comprising the anti-CD30 antibody and a pharmaceutically acceptable carrier (see entire document, particularly pp. 2, 8-10, 12-13 and Example 1). As evidenced by the specification and Nagata et al antibody HeFi-1 binds to epitope IIa (see Tables 1-2 of the instant specification and table 2 of Nagata et al) and epitopes IIa and VI constitute the stalk region of CD30 (specification pg. 15, lines 28-30). Thus, antibody HeFi-1 of Lemke et al necessarily binds epitope IIa and would necessarily bind to the recited amino acid residues of epitope IIa as recited in claim 3. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of anticipation has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985).

With respect to antibody M67, the specification provides evidence that epitope V is located near the cleavage site on the sCD30 side and cleavage might slightly alter the epitope structure (specification pg. 70, lines 21-22 and Fig. 1). It is noted that antibody M67 binds epitope V, the same epitope as antibody T201 (see Fig. 1). Thus, if antibody T201 binds an epitope that is destroyed upon cleavage of sCD30 from intact CD30

(e.g., see claim 6), it is the examiner's position that antibody M67 directed to the same epitope as antibody T201 is an antibody that also possesses the same structural and functional properties as those of the antibodies claimed. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibodies with antibody M67 of Lemke et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed antibodies and antibody M67 of the prior art. See *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). See MPEP 2112.

Thus, Lemke et al anticipate the claims as evidenced by the specification and Nagata et al.

Conclusion

13. Claims 5-6, 10-11, 15-17 and 39 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

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have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643